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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 02/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/069,973	GRIMM ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 December 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *63-95* is/are pending in the application.

4a) Of the above claim(s) *66-68, 76-93* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *63-65,69-75,94 and 95* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicant adds new claims 94-95, which are related to claims 63-65, 69-75 and are not new matter.

Accordingly, claims 63-65, 69-75, 94-95 are being examined.

The following are the remaining rejections.

This application contains claims drawn to an invention nonelected with traverse in Paper of 08/03/04. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

INFORMATION DISCLOSURE STATEMENT

Applicant argues that Applicant is not aware of any requirement that an Applicant withhold an Information disclosure statement until all 371 requirement have been met.

The Examiner takes note that the date of the submission of the information disclosure statement is 03/11/02, which is prior to the filing date of 06/17/02, and therefore the information disclosure statement could not be entered as part of the filed application, and consequently could not be considered at this time.

Applicant is invited to resubmit the information disclosure statement for consideration.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION

Claims 63-65, 69-75 remain rejected under 112, first paragraph, for lack of a clear written description of 1) an inhibitor or antagonist of ANT-1 protein, 2) "adenine nucleotide translocase-1 (ANT-1)" without being accompanied by a sequence identification number, and 3) a signal transduction pathway activated by ANT-1, for reasons already of record in paper of 09/15/05.

New claims 94-95 are rejected for the same reasons of record.

Applicant argues that the claims 63, 73 have been amended to recite that the inhibitors interact directly with ANT-1. Applicant argues that the specification at page 5, para 2 describes such inhibitors and how one would identify.

Applicant argues that new claims 94-95 further define the interaction as comprising binding to the N-terminal domain of ANT-1.

Applicant concludes that the method of apoptosis inhibition recited in the claims is adequately described.

It is noted that page 5, para 2 of the instant application only discloses that N-terminal amino acids (amino acids 1-150 or amino acids 1-200) of ANT-1 is suitable for screening for compounds that inhibit ANT-1. Except for cyclophilin D and bongkreric acid, the structure of numerous claimed inhibitors or antagonists that bind to ANT-1, or the N-terminal domain of ANT-1 is not disclosed.

Applicant's arguments in paper of 12/15/05 have been considered but are found not to be persuasive for the following reasons:

1. Although the claims have been amended to narrow to subgenus of inhibitors or antagonists of ANT-1 that bind directly to either full length ANT-1 or the N-terminal

domain of ANT-1, **the claimed subgenus of inhibitors or antagonists of ANT-1 are not supported by a clear written description.**

The claimed subgenus of inhibitors or antagonists of ANT-1 encompasses numerous structurally diverse chemical or biological molecules, such as a simple or complex organic molecule, a peptide, a peptidomimetic, a protein or a synthetic peptide that binds to ANT-1 or the N-terminal domain of ANT-1, and inhibits the activity of ANT-1. The specification and the claims do not meet the written description requirement, because a representative number of the structure of the organic molecule, the peptide, the peptidomimetic, the protein or the synthetic peptide, or a common structure thereof, is not disclosed.

The specification and the claim only disclose the function of the inhibitors or antagonists for use in the claimed method, which is not adequate to meet the standards as set out in the example of Lilly. The court stated that " (a) written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula, (or) chemical name, of the claimed subject matter sufficient to distinguish it from other materials". Id. At 1567, 43 USPQ2d at 1405.

The court also stated that a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that

distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. **A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is** (emphasis added)..id At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Further, although the specification discloses how to screen for the inhibitory agent for use in the claimed method, however, this does not meet the written description requirement.

The court has held that a description of DNA "'requires a precise definition, such as by structure, formula, chemical name, or physical properties,' not a mere wish or plan for obtaining the claimed chemical invention." Id. (quoting Fiers v. Revel, 984 F.2d 1 164, 1170 (Fed. Cir. 1993)). Therefore, this court has held that statements in the specification **describing the functional characteristics of a DNA molecule or methods of its isolation do not adequately describe a particular claimed DNA sequence** (emphasis added). Instead "an adequate written description of DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself" Id. at 1566-67 (quoting Fiers, 984 F.2d at 1 171).

Further, it is noted that in a recent 2004 court case (Rochester v. Searle. 358 F.3d 916, Fed Cir., 2004) recited' by Appellant, the court states that "even with the three

dimensional of enzymes such as COX-I and COX-2 in hand, it may even now not be within the ordinary skill in the art to predict what compounds might bind to and inhibit them".

The present application is similar to that in Rochester case, in that one cannot predict what organic molecules, what mimetics or which protein, other than an antibody antagonist of ANT-1, that might bind to and inhibit the activity of ANT-1, especially in view that three dimensional structure of ANT-1 or its N-terminal domain is not even disclosed in the specification or known in the art.

In view of the diverse structure of the claimed inhibitors or antagonists of ANT-1, and further in view that there is no disclosure of a common structure for the claimed inhibitors or antagonists of ANT-1, there is no correlation between structure and the function of inhibiting the activity of ANT-1.

Further the disclosed two inhibitors of ANT-1, cyclophilin D and bongkretic acid, are not representative species of the claimed subgenus of inhibitors or antagonists, in view that no common structure between cyclophilin D and bongkretic acid is disclosed.

Thus the specification fails to describe an inhibitor or antagonist of ANT-1, by the standards shown in the examples of Lilly and Enzo.

The specification does not provide an adequate written description of an inhibitor or an antagonist that directly interacts with ANT-1 or its N-terminal domain, that is required to practice the claimed invention, and one of skill in the art would reasonably conclude that Applicant did not have possession of the subgenus inhibitors or antagonists that directly interact with ANT-1 or its N-terminal domain.

Since the specification fails to adequately describe the product, it also fails to adequately describe the method of inhibition of apoptosis or treatment of diseases associated with excessive apoptosis, using said product.

2. Further, the claims do not meet the 112, first paragraph, written description, because the language "adenine nucleotide translocase-1 (ANT-1)", without being accompanied by a sequence identification number, encompasses a family of adenine nucleotide translocase-1, i.e. variants ANT-1, with unknown structure.

Rejection remains, because Applicant did not answer to this issue.

3. In addition, the claims do not meet the 112, first paragraph, written description, because which apoptosis-inducing signal transduction pathway activated by ANT-1 and which proteins involved in the pathway is not disclosed.

Rejection remains, because Applicant did not answer to this issue.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, ENABLEMENT

Claims 63-65, 69-75 remain rejected under 112, first paragraph, for lack of enablement for a method of inhibition of apoptosis or treatment of diseases associated with excessive apoptosis, comprising administering an inhibitor of the activity of adenine nucleotide transferase-1 (ANT-1), which inhibitor directly interacts with ANT-1 or its N-terminal domain, for reasons already of record in paper of 09/15/05.

New claims 94-95 are rejected for the same reasons of record.

A. Incorporation of essential material, ANT-1, for use in the claimed method.

Applicant asserts that the amino acid sequence of ANT-1 and its corresponding DNA sequence are attached hereto. Applicant argues that ANT-1 is well known in the art, and that a publication by Neckelmann et al, 1987, is attached hereto.

Applicant argues that Applicant will consider the amendment of the specification to insert the known sequence and an appropriate accompanying affidavit, upon a specific request by the Examiner.

Applicant's arguments in paper of 12/15/05 have been considered but are found not to be persuasive for the following reasons:

It is noted that the attached amino acid sequence of ANT-1 and its corresponding DNA sequence, as well as a publication by Neckelmann et al, 1987 is not found in the file.

Further, even if the attached amino acid sequence of ANT-1 and its corresponding DNA sequence, as well as a publication by Neckelmann et al, 1987 were found in the file, attaching to the response the amino acid sequence of ANT-1 and its corresponding DNA sequence, as well as a publication by Neckelmann et al, 1987, would not obviate the 112, first paragraph, according to MPEP 6.19.

Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application (See In re Hawkins, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); In re Hawkins, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); In re

Hawkins, 486 F.2d 577, 179 USPQ 167 (CCPA 1973) and see MPEP 6.19 and 6.19.01).

Further, even if Applicant could overcome the above 112, first paragraph, the claims 63-65, 69-75, 94-95 are still rejected under 112, first paragraph, enablement, because the language "adenine nucleotide translocase-1 (ANT-1)", without being accompanied by a sequence identification number, encompasses a family of adenine nucleotide translocase-1, i.e. variants ANT-1, with unknown structure.

Rejection remains, because Applicant did not answer to this issue.

Applicant does not teach how to make and use the claimed variants ANT-1 such that they function as claimed, in view of the unpredictability of protein chemistry, as taught by Bowie et al, Burgess et al, Lazar et al, all of record.

B. Even if Applicant could overcome the above 112, first paragraph, the claims 63-65, 69-75, 94-95 are still rejected under 112, first paragraph, for lack of enablement for: 1) a method for in vivo inhibition of apoptosis in a cell, wherein said cell could be associated with a pathogenic disorder, 2) a method for treating a disease associated with excessive apoptosis, wherein said disease could be a degenerative disease, wherein said degenerative disease could be dilated cardiomyopathy, for reasons already of record in paper of 09/15/05.

Applicant argues that experimental data demonstrating inhibition of ANT-1 induced apotosis by bongkreric acid is attached hereto, and that therefore the amended claims are fully enabled.

Applicant's arguments in paper of 12/15/05 have been considered but are found not to be persuasive for the following reasons:

Rejection remains, because the attached experimental data demonstrating inhibition of ANT-1 induced apoptosis by bongkreric acid is not found in the file, and cannot be considered.

One cannot predict that an inhibitor of ANT-1 or cyclophilin D would be effective in inhibiting apoptosis in vivo, in view that apoptosis is a complex phenomena, wherein there are diverse cell death pathway, which depend on cell type, cell death stimulus, and the concentration of proteins involved in the apoptosis pathway, as taught by Vogel et al, Oltvai et al, and Gottchalk et al, all of record, and further in view of in vivo homeostasis, in which compensatory mechanism could regulate the outcome of apoptosis, as taught by Xu Xin et al, Gottschalk et al, all of record.

Moreover, one cannot predict that cardiomyopathy would be successfully treated by an inhibitor of ANT-1 or cyclophilin D, in view that treatment of cardiomyopathy is unpredictable, as taught by James et al, LaVecchia et al, all of record.

Moreover, even if dilated cardiomyopathy could be treated with an inhibitor of ANT-1, or cyclophilin D, one cannot predict that any disease associated with excessive apoptosise, or any degenerative diseases could be treated with an inhibitor of ANT-1, or cyclophilin D, in view that different diseases have different etiology and characteristics, as taught by Montesano et al, Burmer et al, Busken et al, all of record, and therefore do not predictably response to the same drug.

C. Even if Applicant could overcome the above 112, first paragraph, and even if cyclophilin D could inhibit apoptosis in vivo, the claims 63-65, 69-70, 72-75, 94-95 are still rejected under 112, first paragraph, for lack of enablement for: 1) a method for in vivo inhibition of apoptosis or a method for treating a disease associated with excessive apoptosis, wherein said disease could be a degenerative disease, and wherein said degenerative disease could be dilated cardiomyopathy, comprising administering "a substance capable of inhibiting the activity of ANT-1 or ANT-1 protein antagonist", for reasons already of record in paper of 09/15/05.

Rejection remains, because Applicant did not answer to this issue.

One does not know how to make the claimed numerous inhibitors or antagonists of ANT-1, in view that the present application is similar to that in Rochester case, in that although the structure of ANT-1 is known in the art, except for an antibody antagonist of ANT-1, one cannot predict what mimetics or what small molecule inhibitors that are capable of inhibiting the activity of ANT-1, especially in view that three dimensional structure of ANT-1 is not even disclosed in the specification or known in the art.

Further, **an inhibitor of the activity of ANT-1 encompasses an inhibitor of the ADP/ATP exchange activity of ANT-1**. One cannot predict that an inhibitor of the ADP/ATP exchange activity of ANT-1 could be used for inhibiting of apoptosis, in view of the disclosure in the specification that ANT-1 apoptosis activity does not depend on its known function for ADP/ATP exchange (p.2, lines 29-31).

Rejection remains, because Applicant did not answer to this issue.

D. If Applicant could overcome the above 112, first paragraph rejection, claim 72 is still rejected under 112, first paragraph, for lack of enablement for a method for inhibition of apoptosis, wherein "an apoptosis-inducing signal pathway is inhibited, said pathway is being activated by ANT-1".

Rejection remains, because Applicant did not answer to this issue.

The specification does not discloses which apoptosis-inducing signal pathway is activated by ANT-1.

In view of a lack of a knowledge of which apoptosis-inducing signal pathway is activated by ANT-1, and the proteins involved in said signal pathway, and in view that apoptosis is a complex phenomenon, wherein there are diverse cell death pathways, which depend on cell type and cell death stimulus (Vogel MW et al, 2002, Cerbellum, 1(4): 277-87, of record), one would not know how to make an inhibitor for the apoptosis-inducing pathway that is activated by ANT-1, such that apoptosis would be inhibited.

REJECTION UNDER 35 USC 102(b)

Claims 63-65, 69-70, 72 remain rejected under 35 U.S.C. 102(b) as being anticipated by Fulda et al, Cancer res, 1998, 58(19): 4453-60, for reasons already of record in paper of 09/15/05.

Applicant argues that the claim 63 is amended to recite that the cell is associated with excessive apoptosis, and that the neuroblastoma cells taught by Fulda et al are not cells associated with excessive apoptosis.

Applicant's arguments in paper of 12/15/05 have been considered but are found not to be persuasive for the following reasons:

Fulda et al teach that the neuroblastoma cells to be treated with bongkreric acid has apoptosis induced by doxorubin or betulinic acid (87% and 78 %, respectively specific apoptosis) (p.4454, under Results).

In view that "excessive apoptosis" is not defined in the specification, the neuroblastoma cells taught by Fulda et al seem to be associated with excessive apoptosis.

Further, bongkreric acid is the specific ligand for ANT and binds to ANT (Pei et al, of record, p.1717, second column, second paragraph).

Although the reference does not specifically teach that the treated cells are associated with execessive apoptosis, and that bongkreric acid directly interacts with ANT-1, however, the cells and the inhibitor for use in the claimed metlhod appears to be the same as the prior art treated cells and inhibitor. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable diffrences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Further, although Fulda et al do not teach that an apoptosis-inducing signal transduction pathway is inhibited, said pathway being activated by ANT-1, the claimed method seems to be the same as the method taught by Fulda et al, in view that the method of the prior art comprises the same method steps as claimed in the instant invention using the same composition.

Because the method of the prior art comprises the same method steps as claimed in the instant invention using the same composition, the claimed method is anticipated because the method will inherently lead to the claimed effects. See Ex parte Novitski 26 USPQ 1389 (BPAI 1993).

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, JEFFREY SIEW can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SUSAN UNGAR, PH.D
PRIMARY EXAMINER

MINH TAM DAVIS

February 02, 2005